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Titlel: Novel 8-aza-bicyclo[3.2.1]octane derivatives and their use as monoamine neurotransmitter re-uptake inhibitors

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Økonomi- og Erhvervsministeriet

24 May 2004

Pia Høybye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

NOVEL 8-AZA-BICYCLO[3.2.1]OCTANE DERIVATIVES AND THEIR USE AS MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITORS

TECHNICAL FIELD

This invention relates to novel 8-aza-bicyclo[3.2.1]octane derivatives useful as monoamine neurotransmitter re-uptake inhibitors.

In other aspects the invention relates to the use of these compounds in a method for therapy and to pharmaceutical compositions comprising the compounds of the invention.

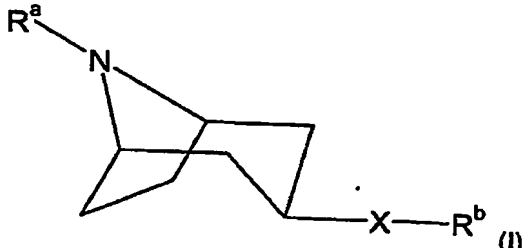
BACKGROUND ART

WO 97/30997 (NeuroSearch A/S) describes tropane derivatives active as neurotransmitter re-uptake inhibitors.

However, there is a continued strong need to find compounds with an optimised pharmacological profile as regards the activity on reuptake of the monoamine neurotransmitters serotonin, dopamine and noradrenaline, such as the ratio of the serotonin reuptake versus the noradrenaline and dopamine activity.

SUMMARY OF THE INVENTION

In its first aspect, the invention provides a compound of the Formula I:



(I)

or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof,

wherein R^a, R^b and X are as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

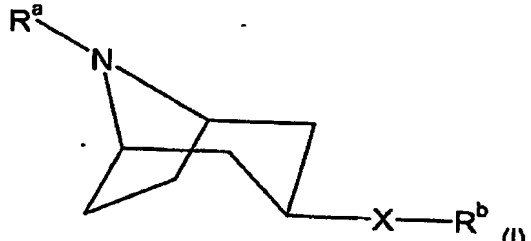
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

8-aza-bicyclo[3.2.1]octane derivatives

In its first aspect the present invention provides compounds of formula I:



(I)

or any of its isomers or any mixture of its isomers,
or a pharmaceutically acceptable salt thereof,
wherein
R^a represents hydrogen or alkyl;
which alkyl is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl;
X represents –O–, –S– or $–NR^c–$;
wherein R^c represents hydrogen, alkyl, $–C(=O)R^d$ or $–SO_2R^d$;
wherein R^d represents hydrogen or alkyl;

R^b represents an aryl or a heteroaryl group,

which aryl or heteroaryl group is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, oxo, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl.

In one embodiment, R^a represents hydrogen or alkyl;

X represents –O–, –S– or $–NR^c–$;

wherein R^c represents hydrogen, alkyl, $–C(=O)R^d$ or $–SO_2R^d$;

wherein R^d represents hydrogen or alkyl;

R^b represents an aryl or a heteroaryl group,

which aryl or heteroaryl group is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl.

In a further embodiment, R^a represents hydrogen or alkyl. In a still further embodiment, R^a represents hydrogen. In a further embodiment, R^a represents alkyl, such as methyl. In a still further embodiment, R^a represents alkyl substituted with hydroxy, cyano, cycloalkyl or alkenyl. In a special embodiment, R^a represents hydroxyalkyl, such as hydroxyethyl. In a further embodiment, R^a represents cyanoalkyl, such as cyanomethyl. In a still further embodiment, R^a represents cycloalkylalkyl, such as cyclopropylmethyl. In a further embodiment, R^a represents alkenylalkyl, such as allyl.

In a further embodiment, X represents –O–. In a still further embodiment, X represents –S–.

In a further embodiment, R^b represents an aryl or a heteroaryl group, which aryl or heteroaryl group is optionally substituted with one or more substituents independently selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano, oxo and alkoxy. In a still further embodiment, R^b represents an aryl or a heteroaryl group, which aryl or heteroaryl group is optionally substituted with one or more substituents independently selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy. In a further embodiment, R^b represents an aryl or a heteroaryl group, which aryl or heteroaryl group is substituted with one or more substituents independently selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano, oxo, alkyl and alkoxy. In a still further embodiment, R^b represents an aryl or a heteroaryl group, which aryl or heteroaryl group is substituted with one or more substituents independently selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano, oxo and alkoxy.In a

further embodiment, R^b represents an aryl or a heteroaryl group, which aryl or heteroaryl group is substituted with one or more substituents independently selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy.

In a further embodiment, R^b represents an unsubstituted, monosubstituted or disubstituted aryl or heteroaryl group.

In a still further embodiment, R^b represents an optionally substituted phenyl group. In a further embodiment, R^b represents an optionally substituted naphthyl group. In a still further embodiment, R^b represents an optionally substituted fluorenyl group.

In a further embodiment, R^b represents an optionally substituted thienyl group. In a still further embodiment, R^b represents an optionally substituted benzoisothiazolyl group.

In a still further embodiment, R^b represents a phenyl group, which phenyl group is optionally substituted with one or more substituents independently selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy.

In a further embodiment, R^b represents a phenyl group optionally substituted once or twice with halo, such as chloro. In a special embodiment, R^b represents phenyl. In a further embodiment, R^b represents a disubstituted phenyl. In a still further special embodiment, R^b represents dichlorophenyl, such as 2,3-dichlorophenyl or 3,4-dichlorophenyl. In a further embodiment, R^b represents phenyl substituted with chloro and fluoro, such as 4-chloro-3-fluorophenyl or 4-fluoro-3-chlorophenyl. In a still further embodiment, R^b represents phenyl substituted with chloro and trifluoromethyl, such as 2-chloro-3-trifluoromethylphenyl or 4-chloro-3-trifluoromethylphenyl. In a further embodiment, R^b represents phenyl substituted with chloro and cyano, such as 3-chloro-4-cyanophenyl. In still a further embodiment, R^b represents phenyl substituted with chloro and methyl, such as 4-chloro-3-methylphenyl. In a further embodiment, R^b represents phenyl substituted with chloro and bromo, such as 4-bromo-3-chlorophenyl. In a further embodiment, R^b represents a monosubstituted phenyl. In a still further embodiment, R^b represents chlorophenyl, such as 3-chlorophenyl or 4-chlorophenyl. In a further embodiment, R^b represents trifluoromethoxyphenyl, such as 3-trifluoromethoxyphenyl or 4-trifluoromethoxyphenyl. In a still further embodiment, R^b represents trifluoromethylphenyl, such as 4-trifluoromethylphenyl. In a further embodiment, R^b represents methylphenyl, such as 4-methylphenyl. In a still further embodiment, R^b represents methoxyphenyl, such as 3-methoxyphenyl or 4-methoxyphenyl. In a still further embodiment, R^b represents cyanophenyl, such as 4-cyanophenyl.

In a further embodiment, R^b represents a naphthyl group, such as 1-naphthyl or 2-naphthyl. In a still further embodiment, R^b represents a naphthyl group substituted once or twice with halo, such as chloro or bromo. In a special embodiment, R^b

represents chloronaphthyl, such as 4-chloronaphthalen-1-yl. In a further embodiment, R^b represents bromonaphthyl, such as 6-bromonaphthalen-2-yl. In a still further embodiment, R^b represents a naphthyl group substituted one or twice with alkoxy, such as methoxy. In a special embodiment, R^b represents methoxynaphthyl, such as 4-methoxynaphthalen-1-yl, 6-methoxynaphthalen-2-yl or 7-methoxynaphthalen-2-yl. In a still further embodiment, R^b represents a naphthyl group substituted one or twice with cyano. In a special embodiment, R^b represents cyanonaphthyl, such as 6-cyanonaphthalen-2-yl.

In a still further embodiment, R^b represents a 1,2,3,4-tetrahydronaphthyl group, such as 1,2,3,4-Tetrahydronaphthalen-6-yl.

In a further embodiment, R^b represents an indanyl group, such as 5-indanyl.

In a still further embodiment, R^b represents a fluorenyl group substituted with oxo, such as fluoren-9-one-2-yl.

In a still further embodiment, R^b represents a thienyl group, which thienyl group is substituted with one or more substituents independently selected from the group consisting of: halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy.

In a further embodiment, R^b represents a thienyl group substituted one or more times with halo, such as chloro. In a special embodiment, R^b represents dichlorothienyl, such as 3,4-dichloro-thiophen-2-yl. In a further special embodiment, R^b represents trichlorothienyl, such as 3,4,5-trichloro-thiophen-2-yl.

In a still further embodiment, R^b represents a benzoisothiazolyl group, such as 1,2-benzoisothiazol-3-yl.

In a further embodiment, R^b represents an optionally substituted benzothiazolyl group. In a special embodiment, R^b represents benzothiazolyl, such as benzothiazol-2-yl. In a further embodiment, R^b represents a benzothiazolyl group substituted once or twice with halo, such as chloro. In a special embodiment, R^b represents chlorobenzothiazolyl, such as 6-chlorobenzothiazol-2-yl.

In a further embodiment, R^b represents a thiazolyl group substituted once or twice with halo, such as bromo. In a special embodiment, R^b represents bromothiazolyl, such as 5-bromothiazol-2-yl.

In a still further embodiment, R^b represents a quinoxalinyl group, such as quinoxalin-2-yl.

In a further embodiment, R^b represents a quinolinyl group, such as quinolin-2-yl, quinolin-6-yl or quinolin-8-yl.

In a further embodiment, R^b represents a isoquinolinyl group, such as isoquinolin-5-yl.

In a still further embodiment, R^b represents a benzoxazolyl group, such as benzoxazol-2-yl.

In a further embodiment, R^b represents an optionally substituted pyridazinyl group. In a still further embodiment, R^b represents a pyridazinyl group substituted once or twice with halo, such as chloro. In a special embodiment, R^b represents chloropyridazinyl, such as 6-chloropyridazin-3-yl.

In a further embodiment, R^b represents an optionally substituted pyridin group. In a still further embodiment, R^b represents a pyridin group substituted once or twice with halo, such as chloro or bromo. In a special embodiment, R^b represents chloropyridin, such as 5-chloropyridin-2-yl or 6-chloropyridin-2-yl. In a further embodiment, R^b represents bromopyridin, such as 5-bromopyridin-2-yl or 6-bromopyridin-2-yl. In a still further embodiment, R^b represents a pyridin group substituted once or twice with alkoxy, such as methoxy. In a special embodiment, R^b represents methoxypyridin, such as 6-methoxypyridin-2-yl.

In a further embodiment, R^b represents a isoquinolinyl group, such as isoquinolin-1-yl.

In a further embodiment, R^b represents an optionally substituted pyrimidin group. In a still further embodiment, R^b represents a pyrimidin group substituted once or twice with halo, such as bromo. In a special embodiment, R^b represents bromopyrimidin, such as 5-bromopyrimidin-2-yl.

In a further embodiment, R^b represents a dibenzofuranyl group, such as dibenzofuran-2-yl.

In a still further embodiment, R^b represents an indolyl group, such as 5-indolyl.

In a special embodiment the chemical compound of the invention is

endo-3-(3,4,5-Trichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
endo-3-(3,4-Dichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3,4,5-Trichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(1,2-Benzoisothiazol-3-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(5-Bromothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Chlorobenzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Quinoxalin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Quinolin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Benzoxazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-chloro-pyridazin-3-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(5-chloro-pyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Isoquinolin-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Chloropyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(5-Bromopyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Bromopyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;

exo-3-(5-Bromopyrimidin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
endo-3-(3,4,5-Trichlorothienyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2,3-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3,4,5-Trichlorothienyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-4-fluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-fluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-phenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2-Chloro-3-trifluoromethyl-phenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Fluoren-9-one-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(1,2-Benzoisothiazol-3-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
endo-3-(3,4-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-trifluoromethylphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2-Dibenzofuranyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(1-Naphthyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2-Naphthyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-4-cyanophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-methylphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloronaphthalen-1-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Quinolin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(5-Chloro-pyridin-2-yl)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Isoquinolin-5-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(6-Bromo-naphthalen-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Bromo-3-chloro-phenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Quinolin-6-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Trifluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Cyanophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Quinolin-8-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methylphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(6-Chloropyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(5-Bromopyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(6-Bromopyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Isoquinolin-1-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3-Trifluoromethoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Trifluoromethoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2,3-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-4-fluorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;

exo-3-(4-Chloro-3-fluorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(2-Chloro-3-trifluoromethyl-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Fluoren-9-one-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(1-Naphthyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(2-Naphthyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-trifluoromethyl-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-4-cyanophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(2-Dibenzofuranyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloronaphthalen-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-methylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(7-Methoxynaphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Methoxynaphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Bromo-3-chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Isoquinolin-5-yl)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Bromo-naphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Methoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Cyanophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(1,2,3,4-Tetrahydronaphthalen-6-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Trifluoromethylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(8-Quinolinyl)-8-methyl-8-azabicyclo[3.2.1]octane;*exo*-3-(5-Indanyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methoxynaphthalen-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Indol-5-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Trifluoromethoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Trifluoromethoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
endo-3-(3,4-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-(cyanomethyl)-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-(allyl)-8-azabicyclo[3.2.1]octane;
exo-3-(6-Methoxypyridin-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Cyano-naphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments as described above is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to six carbon atoms (C_{1-6}-alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl; 1-, 2- or 3-butenyl, or 1,3-butdienyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexdienyl, or 1,3,5-hextrienyl.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butynyl, or 1,3-butdiynyl; 1-, 2-, 3-, 4-pentynyl, or 1,3-pentdiynyl; 1-, 2-, 3-, 4-, or 5-hexynyl, or 1,3-hexdiynyl or 1,3,5-hextriynyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Cycloalkoxy means O-cycloalkyl, wherein cycloalkyl is as defined above.

Cycloalkylalkyl means cycloalkyl as above and alkyl as above, meaning for example, cyclopropylmethyl.

Amino is NH_2 or NH-alkyl or N-$(alkyl)_2$, wherein alkyl is as defined above.

In the context of this invention an aryl group designates a carbocyclic aromatic ring system such as phenyl, naphthyl (1-naphthyl or 2-naphthyl) or fluorenyl The term aryl is also intended to cover a partially hydrogenated carbocyclic aromatic ring system, such as indanyl or 1,2,3,4-tetrahydronaphthyl.

In the context of this invention a heteroaryl group designates an aromatic mono- or bicyclic heterocyclic group, which holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S).

Preferred monocyclic heteroaryl groups of the invention include aromatic 5- and 6 membered heterocyclic monocyclic groups, including for example, but not limited to, oxazolyl (oxazol-2-yl, -4-yl, or -5-yl), isoxazolyl (isoxazol-3-yl, -4-yl, or -5-yl), thiazolyl (thiazol-2-yl, -4-yl, or -5-yl), isothiazolyl (isothiazol-3-yl, -4-yl, or -5-yl), 1,2,4-oxadiazolyl (1,2,4-oxadiazol-3-yl or -5-yl), 1,2,4-thiadiazolyl (1,2,4-thiadiazol-3-yl or -5-yl), 1,2,5-oxadiazolyl (1,2,5-oxadiazol-3-yl or -4-yl), 1,2,5-thiadiazolyl (1,2,5-thiadiazol-3-yl or -4-yl), imidazolyl (2-, 4-, or 5-imidazolyl), pyrrolyl (2- or 3-pyrrolyl), furanyl (2- or 3-furanyl), thienyl (2- or 3-thienyl), pyridyl (2-, 3- or 4-pyridyl), pyrimidyl (2-, 4-, 5- or 6-pyrimidyl), or pyridazinyl (3- or 4-pyridazinyl).

Preferred bicyclic heteroaryl groups of the invention include indolizinyl, in particular 2-, 5- or 6-indolizinyl; indolyl, in particular 2-, 5- or 6-indolyl; isoindolyl, in particular 2-, 5- or 6-isoindolyl; indazolyl, in particular 1- or 3-indazolyl; benzo[b]furanyl, in particular 2-, 5- or 6-benzofuranyl; benzo[b]thienyl, in particular 2-, 5- or 6-benzothienyl; benzimidazolyl, in particular 2-, 5- or 6-benzimidazolyl; benzoxazolyl, in particular 2-, 5- or 6-benzoxazolyl; benzothiazolyl, in particular 2-, 5- or 6-benzothiazolyl; benzoisothiazolyl (1,2-benzoisothiazolyl or 2,1-benzoisothiazolyl), in particular 1,2-benzoisothiazol-3-yl; purinyl, in particular 2- or 8-purinyl; quinolinyl, in particular 2-, 3-, 6-, 7- or 8-quinolinyl; isoquinolinyl, in particular 1-, 3-, 5-, 6- or 7-isoquinolinyl; cinnolinyl, in particular 6- or 7-cinnolinyl; phthalazinyl, in particular 6- or 7-phthalazinyl; quinazolinyl, in particular 2-, 6- or 7-quinazolinyl; quinoxalinyl, in particular 2- or 6-quinoxalinyl; 1,8-naphthyridinyl, in particular 1,8-naphthyridin-2-, 3-, 6- or 7-yl; pteridinyl, in particular 2-, 6- or 7-pteridinyl; and indenyl, in particular 1-, 2-, 3-, 5- or 5-indenyl.

Preferred polycyclic heteroaryl groups of the invention include dibenzofuranyl, in particular 2-dibenzofuranyl.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the

glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the lithium, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

Examples of pre- or prodrug forms of the chemical compound of the invention include examples of suitable prodrugs of the substances according to the invention include compounds modified at one or more reactive or derivatizable groups of the parent compound. Of particular interest are compounds modified at a carboxyl group, a hydroxyl group, or an amino group. Examples of suitable derivatives are esters or amides.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvent such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Steric Isomers

It will be appreciated by those skilled in the art that the compounds of the present invention may contain one or more chiral centers, and that such compounds exist in the form of isomers, i.e. 1R/S, 3R/S and 5R/S.

Moreover, the substituent -X-R^b on position 3 of the 8-aza-bicyclo[3.2.1]octane skeleton of formula I may in particular be in the exo or endo configuration. In one embodiment of the invention the substituent at position 3 is in the exo configuration. In another embodiment of the invention the substituent at position 3 is in the endo configuration.

The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the isomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present

invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. .

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Labelled Compounds

The compounds of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" stands for the binding of a marker to the compound of interest that will allow easy quantitative detection of said compound.

The labelled compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for *in vivo* receptor imaging.

The labelled isomer of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^{2}H (deuterium), ^{3}H (tritium), ^{13}C, ^{14}C, ^{131}I, ^{125}I, ^{123}I, and ^{18}F.

The physical method for detecting the labelled isomer of the present invention may be selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Methods of Preparation

The chemical compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

Compounds of the invention may be tested for their ability to inhibit reuptake of the monoamines dopamine, noradrenaline and serotonin in synaptosomes eg such as described in WO 97/30997. Based on the balanced activity observed in these tests the compound of the invention is considered useful for the treatment the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

In a special embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of: mood disorder, depression, atypical depression, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress disorder, acute stress disorder, drug addiction, drug misuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, pain, inflammatory pain, neuropathic pan, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, premature ejaculation, erectile difficulty, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage or

Gilles de la Tourettes disease. In a preferred embodiment, the compounds are considered useful for the treatment, prevention or alleviation of depression.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

Preferred compounds of the invention show a biological activity in the sub-micromolar and micromolar range, i.e. of from below 1 to about 100 μM.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a chemical compound of the invention.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

General: All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulphate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

Method A

***endo*-3-(3,4,5-Trichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt**

A mixture of tetrachlorothiophene (5.48 g, 24.69 mmol), tropine (*endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol) (3.48 g, 24.69 mmol), potassium-*tert*-butoxide (4.16 g, 37.04 mmol), 18-crown-6-ether (6.53 g, 24.69 mmol) and DMF (50 ml) was stirred at 100°C for 15 h. Aqueous hydrochloric acid (50 ml, 4 M) was added to the mixture. The mixture was washed with diethyl ether (2 x 100 ml). Aqueous sodium hydroxide (100 ml, 4 M) was added. The mixture was extracted with ethyl acetate (3 x 100 ml). The organic phase was washed with aqueous sodium chloride (3 x 50 ml). Yield 2.65 g (33%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 200.4-206.4°C.

***endo*-3-(3,4-Dichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane**

Was prepared according to method A from 2,3,4-trichlorothiophene and tropine (*endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol) isolated as the free base and oil.

***exo*-3-(3,4,5-Trichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane hydrochloric acid salt**

Was prepared according to method A from tetratrichlorothiophene and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 249-250°C.

***exo*-3-(1,2-Benzoisothiazol-3-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane hydrochloric acid salt**

Was prepared according to method A from 3-chloro-1,2-benzoisothiazole and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 259.4-261.2°C.

***exo*-3-(5-Bromothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane**

Was prepared according to method A from 2,5-dibromothiazole and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Isolated as the free base. Mp 104-106°C.

***exo*-3-(Benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method A from 2-chlorobenzothiazole and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 160-162°C.

exo-3-(6-Chlorobenzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 2,6-dichlorobenzothiazole and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 163-164.5°C.

exo-3-(Quinoxalin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 2-chloroquinoxaline and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 208-210°C.

exo-3-(Quinolin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 2-chloroquinoline and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 192.5-195°C.

exo-3-(Benzoxazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 2-chlorobenzoxazole and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 141-144°C.

exo-3-(6-chloro-pyridazin-3-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 3,6-dichloropyridazine and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 181-183°C.

exo-3-(5-chloro-pyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 2,5-dichloropyridine and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 214-216°C.

exo-3-(Isoquinolin-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 1-chloroisoquinoline and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 180-181.5°C.

exo-3-(6-Chloropyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 2,6-dichloropyridine and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 202-204°C.

exo-3-(5-Bromopyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 2,5-dibromopyridine and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 213-215°C.

exo-3-(6-Bromopyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 2,6-dibromopyridine and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 198-200°C.

exo-3-(5-Bromopyrimidin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method A from 5-bromo-2-chloropyrimidine and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 198-200°C.

Method B

***endo*-3-(3,4,5-Trichlorothienyloxy)-8-H-8-azabicyclo[3.2.1]octane**

A mixture of *endo*-3-(3,4,5-trichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane (0.50 g, 1.53 mmol), 1-chloroethyl chloroformate (1.27 ml, 11.5 mmol) and toluene (20 ml) was stirred at reflux for 15 h. Water (10 ml) was added and the was stirred at reflux for 3.5 h. The mixture was evaporated. Sodium methoxide in methanol (5 ml, 1 M) and silica gel 60 (2 g) was added and was followed by evaporation. Chromatography, of the crude mixture, on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound in quantitative yield as free base and oil.

exo-3-(2,3-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane

Was prepared according to method B. Isolated as the free base. Mp 62.3-65.4°C.

exo-3-(3,4-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane hydrochloric acid salt

Was prepared according to method B. Mp 160.1°C.

exo-3-(3,4,5-Trichlorothienyloxy)-8-H-8-azabicyclo[3.2.1]octane hydrochloric acid salt

Was prepared according to method B. Mp 255-256°C.

exo-3-(3-Chloro-4-fluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method B. Mp 151-154°C.

exo-3-(4-Chloro-3-fluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane

Was prepared according to method B. Isolated as free base and oil.

exo-3-(4-Chloro-phenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method B. Mp 188-188.5°C.

***exo*-3-(2-Chloro-3-trifluoromethyl-phenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method B. Mp 190-193°C.

***exo*-3-(Fluoren-9-one-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane**

Was prepared according to method B. Isolated as the free base. Mp 242.8 – 256.3°C.

***exo*-3-(1,2-Benzoisothiazol-3-yloxy)-8-H-8-azabicyclo[3.2.1]octane hydrochloric acid salt**

Was prepared according to method B from 3-chloro-1,2-benzoisothiazole and pseudotropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 252.5°C.

***endo*-3-(3,4-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane hydrochloric acid salt**

Was prepared according to method B from. Mp 287°C.

***exo*-3-(4-Chloro-3-trifluoromethylphenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method B. Mp 215-217°C.

***exo*-3-(2-Dibenzofuranyloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method B. Mp 217-221°C.

***exo*-3-(1-Naphthyloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method B. Mp 223-224°C.

***exo*-3-(2-Naphthyloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method B. Mp 202-204°C.

***exo*-3-(3-Chloro-4-cyanophenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method B. Mp 176.3-178.9°C.

***exo*-3-(4-Chloro-3-methylphenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method B. Mp 192.5-194.5°C.

***exo*-3-(4-Chloronaphthalen-1-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method B. Mp 226-227°C.

***exo*-3-(Quinolin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 211-213°C.

***exo*-3-(5-Chloro-pyridin-2-yl)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 196-198°C.

***exo*-3-(4-Methoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 137-147°C.

***exo*-3-(Isoquinolin-5-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 192-194°C.

***exo*-3-(6-Bromo-naphthalen-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane hydrochloric acid salt**
Was prepared according to method B. Isolated as free base. Mp 270-274°C.

***exo*-3-(4-Bromo-3-chloro-phenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 207-209°C.

***exo*-3-(Quinolin-6-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 237-239°C.

***exo*-3-(4-Trifluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane hydrochloric acid salt**
Was prepared according to method B. Mp 178-180°C.

***exo*-3-(4-Cyanophenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 188.9-191.6°C.

***exo*-3-(Quinolin-8-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 182-184.5°C.

***exo*-3-(4-Methylphenoxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 174-177°C.

***exo*-3-(6-Chloropyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B from 2,6-dichloropyridine and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 202-204°C.

***exo*-3-(5-Bromopyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt**
Was prepared according to method B. Mp 216-218°C.

exo-3-(6-Bromopyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method B. Mp 218-220°C.

exo-3-(Isoquinolin-1-yloxy)-8-H-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method B from 1-chloroisoquinoline and pseudo-tropine (*exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol). Mp 215-217°C.

exo-3-(3-Trifluoromethoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane
Was prepared according to method B. Isolated as the free base. Mp 185.5-187°C.

exo-3-(4-Trifluoromethoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane
Was prepared according to method B. Isolated as the free base. Mp. 192.5-194°C.

Method C

exo-3-(2,3-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Diethylazodicarboxylate (8.36 ml, 53.1 mmol) was added dropwise at room-temperature to a mixture of tropine (*endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol) (5.0 g, 35.4 mmol), 2,3-dichlorophenol (6.93 g, 42.5 mmol), triphenylphosphine (13.9 g, 53.1 mmol) and dioxane (55 ml). The mixture was stirred for 40 h at 100°C. Aqueous sodium hydroxide (100 ml, 1 M) was added to the mixture. The mixture was extracted with dichloromethane (2 x 100 ml). Chromatography on silica gel with methanol, dichloromethane and acetone (1:4:1) gave the title compound. Yield 6.22 g, (61%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 171.3-194.7°C.

exo-3-(3,4-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 225.6°C.

exo-3-(3-Chloro-4-fluorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane
Was prepared according to method C. Isolated as free base and oil.

exo-3-(4-Chloro-3-fluorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane
Was prepared according to method C. Isolated as free base and oil.

exo-3-(2-Chloro-3-trifluoromethylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane
Was prepared according to method C. Isolated as free base and oil.

exo-3-(3-Chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane oxalic acid salt
Was prepared according to method C. Mp 208-209°C.

exo-3-(4-Chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane oxalic acid salt

Was prepared according to method C. Mp 150.5-154.0°C.

exo-3-(Fluoren-9-one-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane hydrochloric acid salt

Was prepared according to method C. Mp Decomp.

exo-3-(3,4-Dichlorophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method C from 3,4-dichlorothiophenol. Mp 179-181°C.

exo-3-(1-Naphthyloxy)-8-methyl-8-azabicyclo[3.2.1]octane

Was prepared according to method C. Isolated as free base. Mp 72-74°C.

exo-3-(2-Naphthyloxy)-8-methyl-8-azabicyclo[3.2.1]octane

Was prepared according to method C. Isolated as free base. Mp 83-86°C.

exo-3-(4-Chloro-3-trifluoromethylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method C. Mp 172.3-174.2°C.

exo-3-(3-Chloro-4-cyanophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method C. Mp 191.7-194.3°C.

exo-3-(2-Dibenzofuranyloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method C. Mp 199.9-202.0°C.

exo-3-(4-Chloronaphthalen-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method C. Mp 198-199°C.

exo-3-(4-Chloro-3-methylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method C. Mp 230-232°C.

exo-3-(4-Methoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method C. Mp 164.5-166.5°C.

exo-3-(7-Methoxynaphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method C. Mp 143-145°C.

exo-3-(6-Methoxynaphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 78.5-81.5°C.

exo-3-(4-Bromo-3-chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 218-220°C.

exo-3-(Isoquinolin-5-yl)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 193-196°C.

exo-3-(6-Bromo-naphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 227-229°C.

exo-3-(3-Methoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 144-147°C.

exo-3-(4-Cyanophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 177.9-181.9°C.

exo-3-(1,2,3,4-Tetrahydronaphthalen-6-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 165.9-167.2°C.

exo-3-(4-Trifluoromethylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 184.1-186.5°C.

exo-3-(4-Methylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 178-181°C.

exo-3-(8-Quinolinyl)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt Was prepared according to method C. Mp 158-160°C.

exo-3-(5-Indanyloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt
Was prepared according to method C. Mp 184.7-185.9°C.

***exo*-3-(4-Methoxynaphthalen-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method C. Mp 185-188°C.

***exo*-3-(Indol-5-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method C. Mp 176.3-178.3°C.

***exo*-3-(3-Trifluoromethoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane**

Was prepared according to method C. Isolated as the free base. Oil.

***exo*-3-(4-Trifluoromethoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane**

Was prepared according to method C. Isolated as the free base. Oil.

Method D

***endo*-3-(3,4-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt**

A mixture of *endo*-3-chloro-8-methyl-8-azabicyclo[3.2.1]octan (3.9, 24 mmol), (prepared from *exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol and thionylchloride at reflux for 3 h), 3,4-dichlorophenol (5.9 g, 36 mmol), sodium hydride 60% (1.2 g, 36 mmol) and ethanol (30 ml) was stirred at reflux for 15 h. Aqueous hydrochloric acid (50 ml, 4 M) was added to the mixture. The ethanol was evaporated The mixture was washed with diethyl ether (3 x 50 ml). Aqueous sodium hydroxide (50 ml, 4 M) was added. The mixture was extracted with diethylether (3 x 50 ml). Chromatography, of the crude mixture, on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.90 g (9%). Mp 198.0-207.7°C.

Method E

***exo*-3-(3,4-Dichlorophenoxy)-8-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane**

A mixture of *exo*-3-(3,4-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane (2.2 g, 8.1 mmol), 2-bromoethanol (0.6 ml, 8.9 mmol), potassium carbonate (1.1 g, 8.1 mmol) and ethanol (20 ml) was stirred at reflux for 15 h. Aqueous sodium hydroxide (50 ml, 4 M) was added. The mixture was extracted with dichloromethane (3 x 50 ml). Chromatography, of the crude mixture, on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base and oil. Yield 0.40 g (16%).

***exo*-3-(3,4-Dichlorophenoxy)-8-(cyanomethyl)-8-azabicyclo[3.2.1]octane fumaric acid salt**

Was prepared according to method E. Mp 79-82°C.

exo-3-(3,4-Dichlorophenoxy)-8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method E. Mp 187-189.5°C.

exo-3-(3,4-Dichlorophenoxy)-8-(allyl)-8-azabicyclo[3.2.1]octane fumaric acid salt

Was prepared according to method E. 202-206°C.

Method F

exo-3-(6-Methoxypyridin-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

A mixture of *exo*-3-(6-Chloropyridin-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane (6.5 g, 25.8 mmol), sodium methoxide (6.5 g, 0.12 mol) and NMP (30 ml) was stirred at 130°C for 15 h. Water (300 ml) was added. The mixture was extracted with diethylether (3 x 150 ml). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 3.0 g (32%). Mp 176-177.5°C.

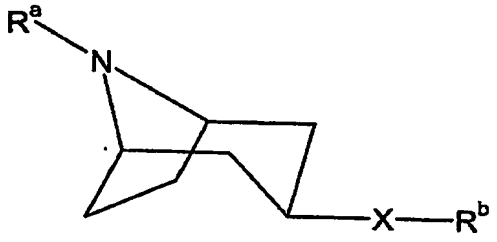
Method G

exo-3-(6-Cyano-naphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane fumaric acid salt

A mixture of *exo*-3-(6-bromo-naphth-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane (2.6 g, 7.5 mmol), Zn(CN)2 (2.2 g, 18 mmol), palladacycle (50 mg) and dioxane (30 ml) was stirred at reflux for 70 h. Aqueous sodium hydroxide (50 ml, 1 M) was added to the mixture. The mixture was extracted with dichloromethane (2 x 50 ml). Chromatography on silica gel with methanol, dichloromethane and aqueous ammonia (1:9:1%) gave the title compound. Yield 2.06 g, (94%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 230-232°C.

CLAIMS

1. A 8-aza-bicyclo[3.2.1]octane derivative of the Formula I:



(I)

or any of its isomers or any mixture of its isomers,
or a pharmaceutically acceptable salt thereof,
wherein
R^a represents hydrogen or alkyl;
which alkyl is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl;
X represents –O–, –S– or $–NR^c–$;
wherein R^c represents hydrogen, alkyl, $–C(=O)R^d$ or $–SO_2R^d$;
wherein R^d represents hydrogen or alkyl;
R^b represents an aryl or a heteroaryl group,
which aryl or heteroaryl group is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, oxo, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl.

2. The chemical compound of claim 1, wherein
R^a represents hydrogen.

3. The chemical compound of claim 1, wherein
R^a represents methyl.

4. The chemical compound of claim 1, wherein
R^a represents 2-hydroxyethyl.

5. The chemical compound of any one of claims 1-4, wherein
X represents –O–.

6. The chemical compound of any one of claims 1-4, wherein
X represents –S–.

7. The chemical compounds of any one of claims 1-6, wherein
R^b represents an aryl or a heteroaryl group,
which aryl or heteroaryl group is substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, trifluoromethoxy, cyano, oxo, alkyl and alkoxy.

8. The chemical compound of any one of claims 1-6, wherein
R^b represents a phenyl group,
which phenyl group is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy.

9. The chemical compound of any one of claims 1-6, wherein
R^b represents a thienyl group,
which thienyl group is substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, trifluoromethoxy, cyano and alkoxy.

10. The chemical compound of any one of claims 1-6, wherein
R^b represents a fluorenyl group substituted with oxo.

11. The chemical compound of any one of claims 1-6, wherein
R^b represents a naphthyl group.

12. The chemical compound of any one of claims 1-6, wherein
R^b represents a benzoisothiazolyl group.

13. The chemical compound of claim 1, which is
endo-3-(3,4,5-Trichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
endo-3-(3,4-Dichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3,4,5-Trichlorothienyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(1,2-Benzoisothiazol-3-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(5-Bromothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Chlorobenzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;

exo-3-(Quinoxalin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Quinolin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Benzoxazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-chloro-pyridazin-3-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(5-chloro-pyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Isoquinolin-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Chloropyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(5-Bromopyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Bromopyridin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(5-Bromopyrimidin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
endo-3-(3,4,5-Trichlorothienyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2,3-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3,4,5-Trichlorothienyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-4-fluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-fluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-phenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2-Chloro-3-trifluoromethyl-phenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Fluoren-9-one-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(1,2-Benzoisothiazol-3-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
endo-3-(3,4-Dichlorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-trifluoromethylphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2-Dibenzofuranyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(1-Naphthyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2-Naphthyloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-4-cyanophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-methylphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloronaphthalen-1-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Quinolin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(5-Chloro-pyridin-2-yl)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Isoquinolin-5-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(6-Bromo-naphthalen-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Bromo-3-chloro-phenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Quinolin-6-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Trifluorophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Cyanophenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Quinolin-8-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methylphenoxy)-8-H-8-azabicyclo[3.2.1]octane;

exo-3-(6-Chloropyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(5-Bromopyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(6-Bromopyridin-2-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(Isoquinolin-1-yloxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(3-Trifluoromethoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(4-Trifluoromethoxyphenoxy)-8-H-8-azabicyclo[3.2.1]octane;
exo-3-(2,3-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-4-fluorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-fluorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(2-Chloro-3-trifluoromethylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane
exo-3-(4-Chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Fluoren-9-one-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenylthio)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(1-Naphthyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(2-Naphthyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-trifluoromethylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Chloro-4-cyanophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(2-Dibenzofuranyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloronaphthalen-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Chloro-3-methylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(7-Methoxynaphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Methoxynaphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Bromo-3-chloro-phenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Isoquinolin-5-yl)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Bromo-naphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Methoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Cyanophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(1,2,3,4-Tetrahydronaphthalen-6-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Trifluoromethylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methylphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(8-Quinolinyl)-8-methyl-8-azabicyclo[3.2.1]octane;*exo*-3-(5-Indanyloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(4-Methoxynaphthalen-1-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(Indol-5-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3-Trifluoromethoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;

exo-3-(4-Trifluoromethoxyphenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
endo-3-(3,4-Dichlorophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-(cyanomethyl)-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-(cyclopropylmethyl)-8-azabicyclo[3.2.1]octane;
exo-3-(3,4-Dichlorophenoxy)-8-(allyl)-8-azabicyclo[3.2.1]octane;
exo-3-(6-Methoxypyridin-2-yl)-8-methyl-8-azabicyclo[3.2.1]octane;
exo-3-(6-Cyano-naphthalen-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane;
or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-13, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

15. Use of the chemical compound of any of claims 1-13, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.

16. The use according to claim 15, for the manufacture of a pharmaceutical pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

17. The use according to claim 16, wherein the disease, disorder or condition is mood disorder, depression, atypical depression, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder, obesity, anxiety, generalized anxiety disorder, eating disorder, Parkinson's disease, parkinsonism, dementia, dementia of ageing, senile dementia, Alzheimer's disease, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, post-traumatic stress disorder, acute stress disorder, drug addiction, drug

misuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction, alcoholism, pain, inflammatory pain, neuropathic pan, migraine pain, tension-type headache, chronic tension-type headache, pain associated with depression, fibromyalgia, arthritis, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, irritable bowel syndrome, post-operative pain, post-stroke pain, drug-induced neuropathy, diabetic neuropathy, sympathetically-maintained pain, trigeminal neuralgia, dental pain, myofacial pain, phantom-limb pain, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, urinary incontinence, stress incontinence, urge incontinence, nocturnal incontinence, premature ejaculation, erectile difficulty, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, post-stroke depression, stroke-induced brain damage, stroke-induced neuronal damage or Gilles de la Tourettes disease.

18. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-13, or any of its isomers or any mixture of its isomers, or a pharmaceutically acceptable salt thereof.